REMARKS

Reconsideration of this application, as amended, is respectfully requested.

I. Amendments to the Claims

Claims 1-2, 6, 21 and 28 have been amended. Claims 3-5, 8-10, 12-20, 22-24 and 26 have been canceled without prejudice or disclaimer, and new claim 31 has been added. Claim 1 has been amended to recite that the sample comprises a plurality of different types of unlabeled target ribonucleic acids, each having a 3' polyadenylyl tail. In addition, the term "said contracting" in claims 1 and 21 has been changed to "said contacting." In addition, the phrase "for the detection of multiple portions of a target nucleic acid, the detection of multiple different target nucleic acids, or both" in claims 1 and 28 has been replaced with "for the detection of said ribonucleic acid targets" in claim 1, and with "for the detection of multiple different target nucleic acids" in claim 28. Further, claim 2 has been amended to recite that the capture nucleic acids of the array of claim 1 are complementary to more than one portion of any given target ribonucleic acid. Claim 6 has been amended to recite that the oligonucleotides bound to the nanoparticles comprise a nucleic acid sequence that is capable of hybridizing with the polyadenylyl tail of the target ribonucleic acids.

In claim 21, the phrase "for the detection of multiple portions of a target ribonucleic acid, the detection of multiple different target ribonucleic acids, or both" has been replaced with "for the detection of multiple different target cDNAs." Further, claim 21 has been amended to recite that the plurality of types of target cDNAs include a polydeoxythymidylyl tail or a synthetic oligonucleotide tail having a predetermined sequence, and that the oligonucleotides bound to the one type of nanoparticles have a sequence that is complementary to at least a portion of the polydeoxythymidylyl tail or a synthetic oligonucleotide tail having a predetermined sequence. Also, the contacting step of claim 21 has been deleted. Claim 28 has been amended to recite that the nanoparticles have bound oligonucleotides that are capable of hybridizing with the polyadenylyl tails, synthetic oligonucleotide tails, or the polydeoxythymidylyl tails of the target nucleic acids. Claims 29 and 30 have been amended to replace the term "The method" with "The kit" so that claims 29 and 30 properly depend from claim 28. Finally, new claim 31 depends from claim 6.

Support for the amendments to claims 1-2, 6, 21 and 28 can be found in the original claims and throughout the specification, for example, page 2, lines 7-30. Support for new claim 31 can be found on page 8, lines 19-21 and page 9, line 26 to page 10, line 10 of the specification. Support

for new claims 32 and 33 can be found in original claims 1, 12, and 13. Accordingly, no new matter has been added as a result of the amendments to the claims.

V. Information Disclosure Statement

The Examiner stated that 41 references submitted but not listed on any Information Disclosure Statement were not considered. These references belong to the Fourth Supplemental Information Disclosure Statement. Applicants have determined that that the Fourth and Sixth Supplemental Information Disclosure Statements and their accompanying PTO-1449 forms were not considered by the Examiner. Applicants are resubmitting copies of the Fourth and Sixth Supplemental Information Disclosure Statements and the PTO-1449 forms. The Fourth and Sixth Supplemental Information Disclosure Statements, their accompanying PTO-1449 forms, and cited references were already received by the Office as evidenced by the attached stamped acknowledgement postcards. Applicants respectfully request that the Examiner consider and initial each of the references cited in the PTO-1449 forms.

VI. Objections to the Drawings

The Examiner objected to the drawings because the Examiner alleged that the figures contain large amounts of text and that the lettered parts and letter cases of the figures do not correspond to the description in the specification.

Applicants respectfully point out to the Examiner that formal figures were submitted on January 31, 2005 in response to the Notice to File Corrected Application Papers dated November 29, 2004. Thus, Applicants respectfully request that the Examiner withdraw the objection to the drawings.

VII. Objections to the Specification and the Sequence Listing

The Examiner objected to the specification because of informalities. Specifically, the Examiner alleged that the application failed to comply with the Sequence Rules in that sequences without SEQ ID NOs appear in the specification on pages 23 to 33.

Applicants respectfully point out to the Examiner that in Applicants' response of October 20, 2004, Applicants submitted a Sequence Listing and amended the specification to include SEQ ID

NOs for each of the sequences on pages 23 to 33 in accordance with 37 C.F.R. §§1.821-1.825. Applicants respectfully request that the Examiner withdraw the objections.

VIII. Objections to the Claims

The Examiner objected to claim 1 alleging that the term "said contracting" should be changed to "said contacting." Applicants have amended claim 1 to change "said contracting" to "said contacting." Thus, Applicants respectfully request that the Examiner withdraw the objection to claim 1.

IX. Claim Rejection under 35 U.S.C §112, second paragraph

The Examiner rejected claims 1-30 for being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Specifically, the Examiner alleged that the phrase "for the detection of multiple portions of a target nucleic acid, the detection of multiple different target nucleic acids, or both" in claims 1 and 28, and the phrase "for the detection of multiple portions of a target ribonucleic acid, the detection of multiple different target ribonucleic acids, or both" in claims 14 and 21 are vague and indefinite. In addition, the Examiner alleged that the recitation of "The method" in claims 29 and 30 is vague and indefinite because the claims depend from claim 28 that is drawn to a kit.

Applicants respectfully disagree with the Examiner that the phrase in claims 1 and 28 are vague and indefinite; however, in order to expedite prosecution of the claims, claims 1 and 28 have been amended as discussed above. In addition, claim 14 has been canceled and claim 21 has been amended as discussed above replacing "ribonucleic acid" with "cDNA." Finally, the phrase "The method" in claims 29 and 30 has been replaced with "The kit" so that claims 29 and 30 properly depend from claim 28. Thus, the claims as amended are definite and particularly claim the subject matter regarded as the invention. Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C §112, second paragraph.

X. Claim Rejection under 35 U.S.C §102(b)

The Examiner rejected claims 1-11,14-18, 20-25, and 27 under 35 U.S.C. §102(b) as allegedly being anticipated by either Taton et al I (J. Am. Chem. Soc. 123: 5164 (2001)) ("Taton I") or Taton et al. II (Science 289: 1757 (2000)) ("Taton II"). The Examiner asserts that each of Taton I and

Taton II teaches sandwich nucleic acids molecular hybridization assay that uses an immobilized capture sequence that hybridizes to a target nucleic acid that in turn hybridizes to an oligonucleotide probe that is attached to a nanoparticle. The Examiner specifically cites Scheme 1 and the first three paragraphs on page 5164 of Taton I, and the abstract, Scheme 1, and pages 1757 to the first paragraph of page 1758 of Taton II.

The Applicants respectfully disagree with the Examiner and submit that the claims as amended are not anticipated by either Taton I or Taton II. As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 1093, 1098 (Fed. Cir. 1983). Accordingly, for Taton I or Taton II to be used as anticipatory reference, each reference alone must describe each and every element of the claims. Applicants respectfully submit that neither Taton I or Taton II can be applied to support an anticipation rejection of the claims because neither Taton I or Taton II describe each and every element of the claims.

The pending claims are directed to a method for detecting or quantitating gene expression in a sample. Claim 1 is directed to a method for detecting or quantitating gene expression in a sample comprising multiple different types of target ribonucleic acids that have 3' polyadenylyl tails. The method further comprises providing a substrate having a plurality of types of capture nucleic acid sequences attached in an array for the detection of the targets; providing nanoparticles having bound oligonucleotides that are complementary to at least a portion of the polyadenylyl tails; contacting the sample, the substrate, and the nanoparticles under conditions effective for hybridization of the target to the capture sequences and hybridization of the targets to the nanoparticles; and observing a detectable change. Claim 21 is also directed to a method for detecting or quantitating gene expression in a sample, wherein the sample comprises multiple types of target cDNAs that have polydeoxythymidylyl tails or synthetic oligonucleotide tails having a predetermined sequence.

Thus, the claims are directed to methods for detecting or quantitating gene expression in a sample wherein the targets have 3' polyadenylyl tails or synthetic oligonucleotide tails, or in the case of cDNAs, polydeoxythymidylyl tails. The invention uses the polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails as a means to attaching a single type of nanoparticle probe, and thereby detecting the captured target nucleic acids. The methods of the

invention eliminates labelling and amplifying the target. The invention allows the detection of many different and highly complex sequences with a single type of nanoparticle that carries a unique sequence. There is no need to reverse transcribe mRNA into target cDNA or to label the cDNA with biotin or any markers. The invention provides for simply extracting mRNA from cells, and without any further manipulation detect expression using a universal nanoparticle probe that can hybridize with the tails. The methods of the invention can be used for complex expression analysis without using a multiplicity of different nanoparticle probes.

Unlike the claims, Taton I does not teach or suggest methods for detecting or quantitating gene expression in a sample wherein the sample comprises target ribonucleic acids that have 3' polyadenylyl tails, or samples comprising cDNAs with polydeoxythymidylyl tails or synthetic oligonucleotide tails of predetermined sequence. The absence of any teaching in Taton I of targets with 3' polyadenylyl tails, polydeoxythymidylyl tails, or synthetic oligonucleotide tails is enough by itself to disqualify Taton I as an anticipatory reference. Nevertheless, Taton I also fails to teach a method for detecting or quantitating targets having 3' polyadenylyl tails, polydeoxythymidylyl tails, or synthetic oligonucleotide tails comprising providing a substrate having capture sequences that hybridize to the targets and nanoparticles having bound oligonucleotides that are complementary to at least a portion of the tails. Thus, Taton I cannot anticipate claims 1 and 21 because Taton I fails to teach or even suggest methods for detecting targets having 3' polyadenylyl tails, polydeoxythymidylyl tails, or synthetic oligonucleotide tails as recited in claims 1 and 21.

Moreover, Taton I also fails to describe methods that use polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails as a means to attaching a single type of nanoparticle probe, and thereby detect different captured target nucleic acids, as the claims recite. Unlike the claims, Taton I describes using different types of nanoparticles to detect different targets, for example, Scheme 1 describes using 50 nm and 100 nm nanoparticles to detect two different targets. Each nanoparticle of Taton I carry oligonucleotides specific to a single target, in contrast to the claims that can detect different targets with a single type of nanoparticle that carries a unique sequence.

The Examiner further cited Scheme 1 and the first three paragraphs on page 5164 of Taton I to support the anticipatory rejection. However, the cited sections of Taton I do not teach or suggest methods for detecting targets having 3' polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails comprising providing a substrate having capture sequences that hybridize

to the targets and nanoparticles having bound oligonucleotides that are complementary to at least a portion of the tails. Nothing in the cited sections of Taton I teach, at a minimum, targets having 3' polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails. Moreover, the cited sections of Taton I also fail to describe methods that use a single type of nanoparticle probe to detect different captured target nucleic acids, as the claims recite. Thus, Taton I cannot serve as an anticipatory reference because Taton I fails to teach each and every element of the claims.

Similarly, Taton II also fails to anticipate the claims because Taton II does not teach methods for detecting targets having 3' polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails comprising providing a substrate having capture sequences that hybridize to the targets and nanoparticles having bound oligonucleotides that are complementary to at least a portion of the tails. Like Taton I and unlike the claims, Taton II also fails to even describe targets having 3' polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails, much less methods to detect and quantitate such targets comprising providing a substrate having capture sequences that hybridize to the targets and nanoparticles having bound oligonucleotides that are complementary to at least a portion of the tails.

Moreover, Taton II also fail to describe methods that use a single type of nanoparticle probe to detect different captured target nucleic acids, as the claims recite. Unlike the claims, Taton II describes using nanoparticles with oligonucleotides that hybridize to a specific target that does not have a tail (see Scheme I in Taton II). Taton II also does not describe detecting different targets using a single type of nanoparticle, in contrast to the claims.

Nevertheless, the Examiner cited the abstract, Scheme 1, and the first paragraph on page 1757 to the first paragraph on page 1758 of Taton II to support the anticipatory rejection. However, nothing in the cited sections teach or suggest methods to detect or quantitate targets having 3' polyadenylyl tails, synthetic oligonucleotide tails, or polydeoxythymidylyl tails as recited in claims 1 and 21. The cited sections also fail to describe methods that use a single type of nanoparticle probe to detect different captured target nucleic acids. Thus, Taton II cannot serve as an anticipatory reference because Taton II fails to teach each and every element of the claims.

For the same reasons that claims 1 and 21 are not anticipated by Taton I or Taton II, dependent claims 2, 6, 25 and 27 are also not anticipated by Taton I and Taton II. In view of the above discussion, Applicants respectfully submit that neither Taton I or Taton II anticipates the

claims. Accordingly, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. §102(b) rejection.

XI. Rejection of Claims 28-30 under 35 U.S.C. §103(a)

Claims 28-30 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Taton I or Taton II in view of Molecular Biology Reagents/Protocols 1992 (United States Biochemical Corporation, 1991, Cleveland, Ohio, pages 218-219) ("Protocols"). The Examiner asserts that each of Taton I and Taton II teaches sandwich nucleic acids molecular hybridization assay that uses an immobilized capture sequence that hybridizes to a target nucleic acid that in turn hybridizes to an oligonucleotide probe that is attached to a nanoparticle. The Examiner specifically cites Scheme 1 and the first three paragraphs on page 5164 of Taton I, and the abstract, Scheme 1, and pages 1757 to the first paragraph of page 1758 of Taton II. Further, the Examiner asserts that Protocols teaches a collection of various components for convenience in the implementation of biochemical processes. The Examiner alleged that it would have been obvious for one of ordinary skill in the art to collect the materials needed in the assays of Taton I and Taton II into a kit as taught by Protocols.

The Applicants respectfully disagree with the Examiner and submit that the claims are not rendered obvious by Taton I or Taton II in view of Protocols. As a threshold matter, the Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1485 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). The reference (or references when combined) must teach or suggest all the claimed limitations. MPEP 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the references, not in the applicant's disclosure. Id. and *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). Thus, contrary to the Examiner's position, the Applicants submit that neither Taton I or Taton II in view of Protocols render

the claims obvious because the references when combined do not teach the claimed invention nor provide a reasonable expectation of success.

Claim 28 is directed to a kit for detecting or quantitating gene expression in a sample that comprises one or more different types of unlabeled target nucleic acids that include polydeoxythymidylyl, synthetic oligonucleotide or polyadenylyl tails. The kit further comprises a substrate having a plurality of types of capture nucleic acid sequences attached in an array for the detection of the targets and one or more types of nanoparticles with bound oligonucleotides that hybridize with the polyadenylyl tails, synthetic oligonucleotide tails, or the polydeoxythymidylyl tails. Claim 29 depends from claim 28 and is directed to kits having gold nanoparticles. Claim 30 also depends from claim 28 and covers kits wherein the capture sequences comprise an oligonucleotide, cDNA, or genomic sequence fragment.

At the outset, Applicants note that the present rejection is based on two primary references (Taton I and Taton II) and one secondary reference (Protocols). For the claims to be obvious, there must be a suggestion or motivation to combine all of the elements from the references. The Office Action did not identify where in the cited art there is a suggestion to combine all the particular elements together to arrive at the claimed invention. Applicants respectfully submit that the cited art does not provide such suggestion or motivation. Without such a suggestion or motivation to combine all the elements together, the presently claimed invention cannot be obvious.

Not only does the cited art fail to provide a suggestion or motivation to combine the elements, one skilled in the art would not be motivated to combine the teachings of the cited art because none of the cited references themselves suggest combining any one or all of the cited references, and there is no evidence of record that one skilled in the art would be motivated to combine the cited references in the absence of such a suggestion. Moreover, even if the cited references could be combined, there is no reasonable expectation that such combination would be successful because the cited references, even if combined, do not teach or suggest all the limitations of the pending claims.

Unlike the claims, Taton I does not teach or suggest a kit for detecting or quantitating gene expression in a sample that comprises one or more different types of unlabeled target nucleic acids that include polydeoxythymidylyl, synthetic oligonucleotide, or polyadenylyl tails. Moreover, Taton I fails to teach or suggest a kit for detecting gene expression in a sample that comprises targets with polydeoxythymidylyl, synthetic oligonucleotide, or polyadenylyl tails and the kit further comprising a

substrate having a plurality of types of capture sequences attached in an array for the detection of targets and one or more types of nanoparticles with bound oligonucleotides capable of hybridizing with the polyadenylyl, synthetic oligonucleotide, or the polydeoxythymidylyl tails of the targets. The deficiencies of Taton I are not cured by Protocols because Protocols also fails to teach or suggest a kit for detecting gene expression in a sample comprising targets with polydeoxythymidylyl, synthetic oligonucleotide, or polyadenylyl tails as recited in claim 28. Accordingly, Taton I alone or in combination with Protocols does not teach or suggest each and every element of the invention of claims 28-30, and one of ordinary skill in the art would therefore not be motivated to combine the references because there is no reasonable expectation that such combination would be successful in producing the claimed invention.

The Examiner further cited Scheme 1 and the first three paragraphs on page 5164 of Taton I to support the obviousness rejection. However, nothing in the cited sections provides a suggestion or motivation to combine Taton I with Protocols to arrive at the invention of the claims. Neither does the cited sections of Taton I in combination with Protocols describe each and every element of the claimed invention, or provide reasonable expectation of success to one of ordinary skill in the art that combining the references would successful produce the claimed invention. Thus, claims 28-30 cannot be obvious over Taton I in view of Protocols.

Similarly, Taton II in combination with Protocols does not render claims 28-30 obvious. Unlike the claims, Taton II does not teach or suggest a kit for detecting gene expression in a sample comprising targets with polydeoxythymidylyl or polyadenylyl tails, and the kit further comprising a substrate having capture sequences for the detection of targets and nanoparticles with bound oligonucleotides that hybridize with the polyadenylyl, synthetic oligonucleotide, or the polydeoxythymidylyl tails of the targets. Like Taton I, the deficiencies of Taton II are not cured by Protocols because Protocols also fails to teach or suggest a kit for detecting gene expression as recited in claims 28-30. The Examiner also cited the abstract, Scheme 1, and pages 1757 to the first paragraph of page 1758 of Taton II to support the obviousness rejection. However, nothing in the cited sections provides a suggestion or motivation to combine Taton II with Protocols to arrive at the invention of the claims. Neither does the cited sections of Taton II in combination with Protocols describe each and every element of the claimed invention, or provide reasonable expectation of success to one of ordinary skill in the art that combining the references would successful produce the claimed invention. Thus, claims 28-30 cannot be obvious over Taton II in view of Protocols.

Moreover, the kit of claims 28-30 is directed to the detection of differents targets having polyadenylyl, synthetic oligonucleotide, or polydeoxythymidylyl tails with a single type nanoparticle probe. Taton I and II alone or in combination with Protocols do not teach the invention of claims 28-30. It is unlikely that Taton I or II in combination with Protocols would result in a kit for detecting targets with a single nanoparticle probe as the claims because Taton I or II requires as many different nanoparticles as there are targets, and Protocols adds nothing to modify Taton I or II to use a single nanoparticle. Taton I or II in combination with Protocols can only be used for a limited number of targets because the conditions must be such as to allow each nanoparticle to hybridize to one of the targets. If there many different targets, as the claims recite, Taton I or II in view of Protocols would require as many conditions as there are targets and nanoparticles, a situation that would make Taton I and II impractical and unworkable. On the other hand, claims 28-30 require only conditions that would allow a single type of nanoparticle to hybridize to either a polyadenylyl, synthetic oligonucleotide, or a polydeoxythymidylyl tail. Thus, one skilled in the art would not be motivated to combine Taton I or II with Protocols because such combination would not result in the invention of claims 28-30. This, claims 28-30 cannot be obvious over Taton I or II in view of Protocols.

In view of the above discussion, Applicants respectfully submit that claims 28-30 are nonobvious over Taton I or Taton II in view of Protocols. The Applicants respectfully request that the Examiner withdraw the obviousness rejection of claims 28-30.

XII. Rejection of Claims 12, 13, 19 and 26 under 35 U.S.C. §103(a)

The Examiner also rejected claims 12, 13, 19 and 26 under 35 U.S.C. §103(a) as being allegedly unpatentable over Taton I or Taton II in view of Applicants' disclosure in the paragraph bridging page 19 and page 20. The Examiner alleged that it would have been obvious for one of ordinary skill in the art to substitute the admittedly old silver nanoparticles and optionally silver staining for the gold nanoparticles of either one of the primary references in order to detect the targets that hybridize to the immobilized capture sequences of either one or the primary references.For purposes of expediting prosecution, Applicants have canceled claims 19 and 26 without prejudice or disclaimer or conceding to the Examiner's rejection.

Regarding claims 12 and 13, Applicants respectfully submit that claims 12 and 13 are not obvious over Taton I or Taton II in view of Applicants' disclosure because neither Taton I or Taton II, or the combination with the references cited in the paragraph bridging pages 19 and 20 of the

specification teach the invention of claim 1, the base claim from which claims 12 and 13 depend. As discussed above, for a claim to be obvious, the reference or references must describe every element of the claim, provide a motivation to combine the references, and provide a reasonable expectation of success that combining the references would produce the claimed invention. Neither Taton I or Taton II teach every element of the invention of claim 1, and the deficiencies are not fixed by the references cited in the paragraph bridging pages 19 and 20 of the specification. As the base claim 1 is not obvious, Applicants respectfully submit that dependent claims 12 and 13 are also not obvious. Accordingly, Applicants respectfully summit that the obviousness rejection of claims 12, 13, 19 and 26 is moot, and request that the Examiner withdraw the rejection.

XIII. Conclusion

In view of the above discussion and amendments, the Applicants respectfully submit that the claims are in allowable condition. A Notice of Allowance is respectfully requested.

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the Applicants' undersigned representative at (312) 913-0001 if the Examiner believes that this would be helpful in expediting prosecution of this application.

Respectfully submitted,

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